

Human Neural Stem Cell Transplantation Rescues Functional Deficits in R6/2 and Q140 Huntington's Disease Mice.

Journal: Stem Cell Reports

Publication Year: 2017

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PubMed link: 29233555

Funding Grants: A hESC-based Development Candidate for Huntington's Disease, A hNSC Development Candidate for Huntington's Disease

Public Summary:

Huntington's Disease (HD) is a devastating genetically inherited neurodegenerative disease caused by a mutation within the Huntingtin protein (HTT). The disease affects movement and causes progressive intellectual decline and psychiatric disturbances. Neuropathology primarily involves degeneration of specific neurons and atrophy of the brain. Currently no disease modifying therapies are available, creating a significant unmet medical need. Effective neurorestorative or neuroregenerative strategies based on human stem cells offer a possible therapeutic strategy. Previously, there has been limited research in evaluating transplantation of human neural stem cells (hNSCs) in genetic mouse models of HD. These cells are readily plentiful and produced in a manner that could be used in human clinical trials. To evaluate the potential of that type of hNSCs, we transplanted cells into the brains of two different HD mouse models. Implanted cells survived, showed potential to differentiate into several neural cell types and provided modification of HD-like behaviors. hNSCs had electrical activity similar to immature neurons and made potential contacts with mouse host nerve cells. Mechanistically, the accumulation of a HTT species associated with disease was substantially reduced by the hNSC treatment and HTT visible aggregates (a hallmark of HD) were also lowered. Finally, improvement was also associated with an increase in a brain specific growth factor. These results suggest that hNSCs may be a promising treatment strategy for HD.

Scientific Abstract:

Huntington's disease (HD) is an inherited neurodegenerative disorder with no disease-modifying treatment. Expansion of the glutamine-encoding repeat in the Huntingtin (HTT) gene causes broad effects that are a challenge for single treatment strategies. Strategies based on human stem cells offer a promising option. We evaluated efficacy of transplanting a good manufacturing practice (GMP)-grade human embryonic stem cell-derived neural stem cell (hNSC) line into striatum of HD modeled mice. In HD fragment model R6/2 mice, transplants improve motor deficits, rescue synaptic alterations, and are contacted by nerve terminals from mouse cells. Furthermore, implanted hNSCs are electrophysiologically active. hNSCs also improved motor and late-stage cognitive impairment in a second HD model, Q140 knockin mice. Disease-modifying activity is suggested by the reduction of aberrant accumulation of mutant HTT protein and expression of brain-derived neurotrophic factor (BDNF) in both models. These findings hold promise for future development of stem cell-based therapies.

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